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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,077	04/15/2004	Martin Stanton	23239-531 CIP	9984

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
08/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,077	STANTON ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) *5,7-9 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Election/Restrictions

Claims 5, 7-9 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 24, 2006.

Claims 1, 4, 6, 10 and 13-18 are examined on the merits.

Claim Rejections - 35 USC § 103

Claims 1, 4, 6, 10 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warren in view of Holmes, Apelgren et al. and Virtanen et al. (all of record).

The claimed invention is directed to aptamer-toxin conjugates comprising aptamers conjugated to cytotoxic moieties that can be small molecule chemotherapeutic agent and can be covalently conjugated. In some embodiments the aptamers target tumor cells and the linker comprises nucleophilic or electrophilic moieties. Other embodiments recite the particular structures of the alkaloid vinblastine and the linkers.

Warren discloses at pages 17-18 prodrugs comprising an aptamer and a drug joined by a linker. Warren discloses at pages 26-27 that the drugs include vinca alkaloids. Example 5 describes use of the disclosed prodrugs to target cancerous cells.

In table 4 Warren specifically teaches that the drug can be the vinca alkaloid vinblastine. At page 7 Warren teaches that aptamers have been used as an alternative to antibodies for the purpose of targeting therapeutic agents to cells. Warren does not explicitly teach aptamers targeted to PSMA, the use of the vinblastine analog desacetylvinblastine-3-carboxhydrazide or the use of linkers that comprise dendrimers.

Holmes teaches that PSMA is a transmembrane protein specific to prostate epithelial cells that is expressed at increased levels in cancerous cells. Holmes further teaches that this protein is an ideal sentinel molecule for targeting prostate cancer cells.

Apelgren et al. teach that antibodies conjugated to 4-desacetylvinblastine-3-carboxhydrazide were known in the art to regress adenocarcinoma and squamous carcinoma xenografts in athymic nude mice. Apelgren et al. extend the use of such conjugates to the treatment of ovarian cancer. Apelgren et al. teach that the use of the conjugated drug increased the survival of tumor bearing mice over treatment of the drug alone or a non-antigen binding immunoconjugate.

Virtanen et al. teach complexes containing a binding molecule such as an antibody, a joining component and a therapeutic molecule such as a drug. At column 10 Virtanen et al. teach that the joining component may be a bifunctional linker and may be a dendrimer type polymer.

It would have been obvious to one of ordinary skill in the art at the time of invention to make aptamer-drug conjugates as taught by Warren using an aptamer that targets PSMA. It would have been further obvious to use desacetyl-3-carboxhydrazide as the drug component of the conjugate and to use a dendrimer as the linker component. Holmes provides a motivation to target PSMA with therapeutic agents,

teaching that this protein is preferentially expressed in prostate tissue and expressed at increased levels in cancerous cells. Warren explicitly teaches vinblastine as the drug component of an aptamer-drug conjugate and Apelgren et al. provide a motivation to use desacetylvinblastine-3-carboxhydrazide by teaching that immunoconjugates comprising this drug increase survival time of tumor bearing mice over those receiving the drug alone. Based the teachings of Virtanen et al. one of ordinary skill in the art would recognize that the use of a dendrimer linker is mere design choice made by the person of ordinary skill in order to produce a conjugate with the optimum properties for the desired application. One of ordinary skill in the art would have had a reasonable expectation of success in targeting PSMA with the conjugates taught by Warren because Warren teaches aptamer-drug conjugates, their general applicability and methods of synthesis. One of ordinary skill in the art would have had a reasonable expectation of success in making aptamer-drug conjugates comprising desacetylvinblastine-3-carboxhydrazide or dendrimers because Warren teaches the production of aptamer-drug conjugates, Apelgren et al. teach the synthesis of conjugates comprising desacetylvinblastine-3-carboxhydrazide and Virtanen et al. teach that dendrimers are a known linking moiety that can be incorporated into a conjugate using known synthetic methods.

Thus, the invention of claims 1, 4, 6 10 and 13-18 would have been obvious, as a whole, at the time of invention.

Response to arguments

Applicants traverse the 103 rejection by arguing that without the benefit of the instant application as a road map, one of ordinary skill in the art would not have been able to recapitulate the claimed embodiments of the present invention; apparently arguing that the rejection is based on impermissible hindsight. This is not persuasive because as noted in MPEP 2145, any obviousness rejection is in a sense necessarily a reconstruction based on hindsight reasoning and is not improper if it takes into account only knowledge within the level of ordinary skill in the art at the time the claimed invention was made. Applicants have provided no evidence that the rejection is not based on knowledge available to those of ordinary skill in the art.

Applicants refer to the decision in *Takeda v. Alphapharm* to argue that a specific motivation to make the claimed compounds is required. This is not persuasive because the chemical compounds referred to in this decision are not the same type of compound as in the instant claims. In *Takeda* the court analyzed the obviousness of modifying one prior art small molecule chemical structure with a particular modification at one specific position; the court found that obviousness requires a particular reason to lead one to modify one species to another, different species in order to produce lead compounds for a particular therapeutic purpose. The instant claims, however, are not directed to a particular species and the combination of the cited references is not based on making a particular modification to a known compound, but to substituting an aptamer to a different protein in a known conjugate of aptamer and cytotoxic moiety.

Applicants argue Warren defines a prodrug as a compound that exhibits pharmacological activity after undergoing a chemical transformation in the body and

therefore cannot provide a specific motivation to design an anti-PSMA aptamer to deliver an active cytotoxic agent to a PSMA expressing cell because Warren teaches delivery of inactive prodrugs to a tissue compartment. Applicants further argue the prodrugs in Warren cannot be considered cytotoxic moieties because these prodrugs require some post-administration "chemical transformation" to become therapeutic.

These arguments are not persuasive because regardless of how Warren defines his compounds and envisions their use, the compounds taught in Warren have the same structural limitations as the instant application; an aptamer conjugated to a cytotoxic moiety. It is further noted that the compounds of Warren are not themselves cytotoxic moieties, they comprise cytotoxic moieties, evidenced by the explicit teaching by Warren of the vinca alkaloid vinblastine.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 6, 10, 13 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Lupold et al. (US 2002/0119473) as evidenced by Warren (US 6,610,841).

The claims are directed to aptamer-toxin conjugates comprising aptamers conjugated to cytotoxic moieties that can be a small molecule chemotherapeutic agent and can be covalently conjugated. In specific embodiments the conjugate comprises a linker and the cytotoxic moiety is a vinca alkaloid.

Lupold et al. disclose nucleic acid ligands (aptamers) to PSMA. At paragraph 70, Lupold et al. disclose that these nucleic acid ligands can be used to deliver therapeutic compounds such as cytotoxic compounds and disclose that the therapeutic compound may be covalently bound to a variety of positions on the PSMA nucleic acid ligand and that attachment of the therapeutic agent can be done directly or with the utilization of a linker. Lupold et al. further incorporate by reference the disclosure of application serial number 08/993,765, which issued to Warren as US 6,610,841. Warren discloses conjugates of nucleic acid ligands to the vinca alkaloids at column 18 and the specific alkaloid vinblastine in table 4.

Thus, Lupold et al. disclose all limitations of and anticipate claims 1, 4, 6, 10, 13 and 14.

Claim Rejections - 35 USC § 103

Claims 1, 4, 6, 10 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lupold et al. as evidenced by Warren as applied to claims 1, 4, 6, 10, 13 and 14 above, and further in view of Apelgren et al. (of record) and Virtanen et al. (of record).

Claims 1, 4, 6, 10, 13 and 14 are described in the previous rejection. Claims 15-18 recite the particular structures of the alkaloid vinblastine and the linkers.

The teachings of Lupold et al. are described in the 102 rejection above. Lupold et al. teach conjugates of PSMA and a cytotoxic moiety that is a vinca alkaloid, but does not teach the use of the vinblastine analog desacetylvinblastine-3-carboxhydrazide or the use of linkers that comprise dendrimers.

Apelgren et al. teach that antibodies conjugated to 4-desacetylvinblastine-3-carboxhydrazide were known in the art to regress adenocarcinoma and squamous carcinoma xenografts in athymic nude mice. Apelgren et al. extend the use of such conjugates to the treatment of ovarian cancer. Apelgren et al. teach that the use of the conjugated drug increased the survival of tumor bearing mice over treatment of the drug alone or a non-antigen binding immunoconjugate.

Virtanen et al. teach complexes containing a binding molecule such as an antibody, a joining component and a therapeutic molecule such as a drug. At column 10 Virtanen et al. teach that the joining component may be a bifunctional linker and may be a dendrimer type polymer.

It would have been obvious to one of ordinary skill in the art at the time of invention to substitute desacetyl-3-carboxhydrazide as the vinca alkaloid drug component in the PSMA aptamer-drug conjugates taught by Lupold et al. and also would have been obvious to use a dendrimer as the linker component. Lupold et al. provide a motivation to produce a PSMA aptamer as a conjugate that comprises a vinca alkaloid by specifically incorporating the teachings of Warren (US 6,610,841). Apelgren et al. provide a motivation to use desacetylvinblastine-3-carboxhydrazide in a drug conjugate by teaching that immunoconjugates comprising this drug increase survival time of tumor bearing mice over those receiving the drug alone. Based the teachings of

Virtanen et al. one of ordinary skill in the art would recognize that the use of a dendrimer linker is mere design choice made by the person of ordinary skill in order to produce a conjugate with the optimum properties for the desired application. One of ordinary skill in the art would have had a reasonable expectation of success in making aptamer-drug conjugates comprising desacetylvinblastine-3-carboxhydrazide or dendrimers because Lupold et al. teach the production of aptamer-drug conjugates, Apelgren et al. teach the synthesis of conjugates comprising desacetylvinblastine-3-carboxhydrazide and Virtanen et al. teach that dendrimers are a known linking moiety that can be incorporated into a conjugate using known synthetic methods.

Thus, the invention of claims 1, 4, 6 10 and 13-18 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Primary Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635

Notice of References Cited	Application/Control No. 10/826,077	Applicant(s)/Patent Under Reexamination STANTON ET AL.	
	Examiner Tracy Vivlemore	Art Unit 1635	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2002/0119473	08-2002	Lupold et al.	435/6
*	B	US-6,610,841	08-2003	Warren, Stephen	536/25.3
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
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FOREIGN PATENT DOCUMENTS

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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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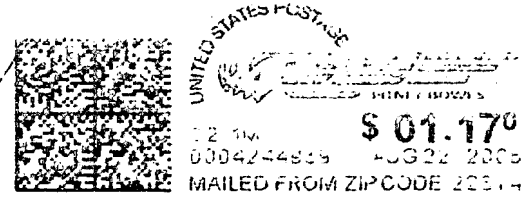

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